REMARKS

In view of the preceding amendments and the comments which follow, and pursuant to 37 CFR §1.111, amendment and reconsideration of the Official Action of April 11, 2006 is respectfully requested by Applicants.

Claim 1 has been amended. Claims 9-19 are new. Support for the amendment to claim 1 is found on page 6, paragraph [0025]. Support for claim 9 is found in the specification on page 6, paragraph [0025]. Support for claims 10-12 is found in the specification on page 7, paragraph [0030]. Support for claim 13 is found in the specification on page 7, paragraph [0031]. Support for claim 14 is found in the specification on page 7, paragraph [0030] and Example 1.3. Support for claim 15 is found in the specification in paragraphs [0015] and [0025] and in original claim 1. Support for claim 19 is found in the specification in Example 1.3. No new matter has been added.

Claims 1-3, 5 and 9-19 are currently pending for examination.

Claim objections

The examiner has objected to claim 1 because the recitation "adjusting the pH…to 10.5 to 12.5" is grammatically awkward. The examiner suggests that the claim recite "adjusting the pH…to between 10.5 and 12.5".

The examiner has also suggested that in claim 1, the adjective "polystyrene" be included with the first reference to "microparticles" in the body of the claim in order to maintain consistency with the preamble.

Applicants have amended claim 1 in accordance with the examiner's suggestions, and they respectfully request the examiner's reconsideration.

Rejections under 35 USC §112, first paragraph

Claims 1-3 and 5 have been rejected under 35 USC §112, first paragraph, as failing to comply with the written description requirement. The examiner argues firstly that claim 1 as originally filed recited combining a suspension of uncoated microparticles with a protein where the suspension comprised a buffer having a pH of 10 to 12.5; however, the claim now recites the

step of adjusting the pH of the combination to between pH 10.5 to 12.5. The examiner argues that when the pH range of 10.5 to 12.5 is mentioned in the specification, it is in the context of coating intervals of 4-7 days; however, claim 1 now recites a pH range of 10.5 to 12.5 and incubating "for a period of time" but makes no mention of a time interval of 4-7 days. The examiner argues that this is broader than the disclosure.

Secondly, the examiner argues that the incorporation of the step of adjusting the pH into claim 1 has effectively created a new subgenus that is not supported by the specific teaching of particular types of microparticles, a particular protein, and a particular pH range. The examiner argues that there is no support in the specification for the step of adjusting the pH to between 10.5 and 12.5 since the specification only discloses adjusting the pH to between 10 and 12.5.

Thirdly, the examiner argues that claim 2 as originally filed recited that the protein is in a polymerized form. The amendment filed 10/6/05 amended the claim to recite that the protein has been polymerized by chemical treatment; however, the examiner argues that this limitation is deemed to represent new matter. The examiner argues that the specification provides support for polymerized streptavidin (and possibly also avidin) that has been polymerized by chemical treatment, but there is no generic teaching of polymerization of proteins in general by chemical treatment.

Claim 1 has now been amended by removing the limitation of adjusting the pH. This limitation is now recited in dependent claims 14 and 19. Applicants argue that the examiner has apparently confused the notion of alternative embodiments and the concept of a "sub-genus". The Summary of the Invention clearly states that the application is directed to a method wherein microparticles are loaded with a protein under strongly alkaline pH conditions. The coating is preferably carried out at a pH selected from the range of 10.0 and 12.5. As such, the pH of 10.5 to 12.5 falls within that range and thus conforms to the stated objective of the summary of the invention. This is simply an alternative pH range suitable for use with the invention.

Secondly, the examiner seems to argue that the smaller pH range is associated with coating intervals of 4-7 days. Applicants argue that this narrow interpretation of the specification is a mischaracterization of the objective teaching of the specification. First, paragraph 30 of the specification teaches that coating incubation times can range from 1-10 days or for 4-7 days.

"When using these relatively long time intervals, pH ranges of 10.5 to 12.5 and in particular of 11.0 to 12.0 are particularly preferred." Note the quoted sentence of paragraph 30 refers to the plural form ("these") of time intervals, indicating that the sentence was referencing the time 4-7 days as stated in the immediately preceding sentence and the interval of 1-10 days as stated in next immediately preceding sentence. Thus the pH range of 10.5 to 12.5 at a bare minimum is associated with a time interval of 1-10 days. Second, the quoted sentence also states that these ranges are preferred, not mandated. This is particularly relevant because in Example 1.3, the time interval used was 4-7 days and yet the cited pH range used in that example is 10.0 to 12.5, thus signifying the interchangeability (alternative embodiments) of the two specifically recited pH ranges.

The Examiner cites Ex parte Westphal and In re Smith as supporting her position that disclosure of a genus and species of a subgenus within that genus is not sufficient description of subgenus to satisfy the written description requirement of 35 USC 112, unless there are specific facts which lead to the determination that a subgenus is implicitly described. As emphasized in Ex parte Westphal and In re Smith, it is necessary to make the relavant determination based on the facts of each case. Ex parte Westphal is distinguished from the present application in that Ex parte Westphal attempted to selectively choose one particular cited range from a list of many ranges cited in the various examples. This selective choosing from a laundry list of ranges to create new subgenuses is prohibited by 35 USC 112. However, Applicants have merely described an alternative pH range that is interchangeable with the only other pH range cited in the specification, as shown by the examples. Thus the facts of the present case indicate that the two pH ranges were intended to be alternative embodiments of pH ranges suitable for use in the described invention which relates to loading proteins onto microparticles under "strongly alkaline pH conditions."

With regard to the examiner's argument that the recitation in claim 2 of a protein that has been polymerized is not supported by the disclosure of "streptavidin polymerized by chemical treatment", Applicants argue that compliance with 35 USC §112 does not require that applicants include in their specification that which is known to the skilled practitioner. The use of chemical treatments to polymerize proteins is a well established field and applicants are not required to recite that which is known. In support of this position, please refer the Examiner to MPEP 2163.05 (I.) Addition of Generic Claim. A single disclosed species can be sufficient to support a

genus claim, when coupled with common knowledge of the skilled practitioner. A disclosure of a composition comprising corticosteroid in DMSO was found sufficient to support claims to a method of using a mixture of a "physiologically active steroid" and DMSO [In re Herschler, 591 F.2d 693, 697 (CCPA 1979)].

In light of the present amendments and the above remarks, the examiner's reconsideration of the rejection under 35 USC §112, first paragraph, is respectfully requested by Applicants.

Rejection under 35 USC §112, second paragraph

Claims 1-3 and 5 have been rejected under 35 USC §112, second paragraph, as being indefinite in the recitation, in claim 1, of "the combination" in part (b). There is insufficient antecedent basis for this limitation in the claim.

Applicants have now amended claim 1 so that an antecedent problem is avoided.

In light of the present amendments and the above remarks, the examiner's reconsideration of the rejection under 35 USC §112, second paragraph, is respectfully requested by Applicants.

Rejections under 35 USC §103 (a)

Claim 1 has been rejected under 35 USC §103 (a) as being unpatentable over Vaynberg et al., *Biomacromolecules 1*, 466-472, 2000 (hereinafter "Vaynberg") in light of Bocquier et al., *Structure 7*, 1451-1460, 1999 (hereinafter "Bocquier") and Bohidar, Int. J. Biol. Macromolecules 23:1-6, 1998 (hereinafter "Bohidar"). The examiner argues that Vaynberg teaches a method for producing protein-coated polystyrene microparticles that includes the steps of combining a suspension (colloid) of uncoated microparticles with a polymerized protein that is a member of a bioaffinity binding pair (gelatin), the combination comprising a buffer of pH 10, incubating the combination for a period of time whereby the protein is coated onto the microparticles by adsorption, and separating the non-adsorbed protein from the protein-coated microparticles (by centrifugation). Vaynberg does not specifically recite a reaction pH of pH 10.5 to 12.5 but teaches adsorption of gelatin onto polystyrene particles at various pH values up to pH 10. The examiner argues that it would have been obvious to one of ordinary skill in the art to employ slightly higher pH values, e.g., pH 10.5, through routine optimization/experimentation of the conditions of Vaynberg with a reasonable expectation of success. She argues that one would be

motivated to employ higher pH values because Vaynberg teaches that because hydrophobic effects dominate in adsorption of gelatin, increasing pH enables a denser layer of gelatin to form on the polystyrene. The examiner argues that one would have a reasonable expectation of success in employing higher pH values in the method of Vaynberg because Vaynberg repeatedly teaches that pH differences were not critical and produced little variation in the adsorption efficiency of gelatin onto the polystyrene.

The examiner relies upon the Bocquier and Bohidar references for their teaching that the protein of Vaynberg fulfills the limitations of being a partner of a bioaffinity binding pair and having a size for 10 nm to 300 nm as recited in claim 1.

Applicants traverse the rejection and argue firstly that neither Vaynberg, Bocquier, nor Bohidar teach or suggest a pH range of 10.5 to 12.5. The examiner argues that it would be obvious to employ "slightly higher" pH values, e.g., pH 10.5 through routine optimization because of the normal desire of scientists to improve upon what is already generally known. The examiner cites MPEP 2144.05 which notes that "a prima facie case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties." Applicants point out that there is a large difference in pH between 10.0 and 10.5, a difference large enough that pH 10.5 would not reasonably be considered to be "close enough" or "slightly higher" than pH 10.0 by the skilled artisan.

The examiner argues that one would have a reasonable expectation of success in employing higher pH values in the method of Vaynberg because Vaynberg repeatedly teaches that pH differences were not critical and produced little variation in the adsorption efficiency of gelatin onto the polystyrene. Applicants point out, however, that Vaynberg never teaches anything beyond pH 9.0 with regard to adsorption, and specifically teaches that maximum adsorption was obtained at pH 6.2. The Examiner contends that that Vaynberg suggests that although a maximum adsorption was obtained at 6.2 the general teaching of the reference was that pH just wasn't that important. Even if one accepts the examiner's interpretation of Vaynberg, this certainly would not provide motivation for one to experiment with higher pH's than those tested by Vaynberg when attempting to obtain better adsorption. An objective reading of

Vaynberg either teaches that the maximum adsorption is obtained a pH 6.2 or that pH just does not matter when coating polystyrene microparticles.

The examiner makes note that a higher pH of up to 10.0 was found to result in "swelling of the layer with increase pH," but the examiner fails to explain how such disclosure would motivate someone who is attempting to adsorb more material with less bleeding onto a microparticle to modify Vaynberg to create applicants claimed method. Thus the examiner has failed to provide any motivation for coating microparticles at a high alkaline pH of 10.0-12.5, and the teaching is even further removed from suggesting coating polystyrene microparticles at a pH range of 10.5 to 12.5. Applicants were the first to describe the "pronounced" increase in the measured signal with proteins coated under strong alkaline conditions (paragraph [0016]), and this is what lead to the presently claimed invention.

Applicants note that at most, one might argue that Vaynberg provides an invitation to experiment; however, "obvious to try" is not the proper standard for obviousness. An obvious-to-experiment standard is not an acceptable alternative for obviousness. There must be a reason or suggestion in the art for selecting the procedure used, other than knowledge learned from the applicant's disclosure. In re Dow Chemical Co., 837 F2d 469 (Fed. Cir. 1988). There is simply no suggestion in Vaynberg that would motivate one of ordinary skill to try and enhance adsorption by using a high alkaline pH during the coating procedure.

In light of the present amendments and the above remarks, the examiner's reconsideration of the rejection of claim 1 under 35 USC §103 is respectfully requested by Applicants.

Claim 2 has been rejected under 35 USC §103 (a) as being unpatentable over Vaynberg in light of Boequier and Bohidar as applied to claim 1, and in view of Tischer et al., U.S. Patent No. 5,061,640 (hereinafter "Tischer"). The examiner argues as previously with regard to Vaynberg, and she adds that Vaynberg fails to teach a protein that has been polymerized by chemical treatment. Tischer teaches polymerizing of proteins to be adsorbed using a cross-linking compound, which has the effect of increasing their molecular weights which results in improved adsorption of the proteins onto the insoluble carrier material. Therefore it would have been obvious to include the step of polymerizing gelatin by treatment with a cross-linking compound as taught by Tischer in the method for producing protein-coated microparticles of Vaynberg in

order to increase the molecular weight of gelatin and thereby improve the adsorption of gelatin to polystyrene.

Applicants traverse and argue that claim 2 depends from claim 1, whose patentability over Vaynberg has been argued above. The Tischer reference does not make up for the deficiencies of Vaynberg as a reference under 35 USC §103 (a), and therefore claim 2 should enjoy the same patentability as claim 1.

In light of the present amendments and the above remarks, the examiner's reconsideration of the rejection of claim 2 under 35 USC §103 is respectfully requested by Applicants.

Claim 3 has been rejected under 35 USC §103 (a) as being unpatentable over Vaynberg in light of Bocquier and Bohidar as applied to claim 1, and in view of Desai et al., U.S. Patent No. 6,638,728 (hereinafter "Desai"). The examiner argues as previously with regard to Vaynberg, and she adds that Vaynberg fails to teach a method where the protein coated is streptavidin that has been polymerized by chemical treatment. Desai teaches methods for producing surfaces such as polystyrene spheres that are coated with streptavidin that has been polymerized by treatment with a chemical cross-linking reagent and that such surfaces are useful in capturing target molecules in assays. Therefore it would have been obvious to employ the method for producing protein-coated polystyrene microparticles of Vaynberg to coat streptavidin that has been polymerized by chemical treatment as taught by Desai in order to produce microparticles that have a high capacity for capturing target molecules for use in assays.

Applicants traverse and argue that claim 3 depends from claim 1, whose patentability over Vaynberg has been argued above. The Desai reference does not make up for the deficiencies of Vaynberg as a reference under 35 USC §103 (a), and therefore claim 3 should enjoy the same patentability as claim 1.

In light of the present amendments and the above remarks, the examiner's reconsideration of the rejection of claim 3 under 35 USC §103 is respectfully requested by Applicants.

Claims 1-2 have been rejected under 35 USC §103 (a) as being unpatentable over Lou et al., U.S. 4,329,151 (hereinafter Lou) in light of Rossjohn et al., Cell 89:685-692, 1997 (hereinafter Rossjohn) and Weis et al., Biochim. Biophys. Acta 1510:292-299, 2001 (hereinafter

Weis). The examiner argues that Lou teaches a method for producing protein-coated polystyrene latex microparticles comprising combining a suspension of polystyrene latex particles with a protein (streptolysin-O) and further teaches incubating the combination of microparticles and protein in a buffer solution with a pH range from about 8.5 to 11.9 for a period of time whereby the protein is coated onto the microparticles by adsorption. Lou further teaches separating the non-adsorbed protein from the protein-coated microparticles by a wash step followed by centrifugation of the particles. The examiner states that Lou fails to teach the step of adjusting the pH of the microparticle-protein combination. It is the examiner's position that it would have been obvious to one of ordinary skill in the art that maintaining the pH of the microparticle-protein combination during the coating reaction could be performed in several ways in order to achieve this same desired result.

The examiner also states that Lou fails to specifically state that the streptolysin-O has a size from 10 nm to 300 nm. However, the examiner posits, based upon teachings of Rossjohn and Weis, that, while it appears that the exact size of streptolysin-O has not been determined by X-ray crystallography, Weis teaches that the X-ray structure of another member of the class of thiol-activated toxins, perfringolysin-O, has been determined. The examiner then takes the dimensions of perfringolysin-O (115 x 30 x 55 Angstroms) and multiplies them by 0.1 nm to conclude that the dimensions of perfringolysin-O (11.5 x 3 x 5.5 nm) fall within the claimed size range of 10 nm to 300 nm and that therefore, the dimensions of streptolysin-O also fall withing the claimed size range.

With regard to claim 2, the examiner argues that the streptolysin-O protein of Lou is polymerized (cross-linked) by addition of a carbodiimide compound.

Applicants traverse the rejection and argue that the examiner's case for *prima facie* obviousness has not been made. Applicants teach on page 6, paragraph [0025], that the protein has a size of at least 10 nm up to a maximum of 300 nm as determined by photon correlation spectroscopy, and that a size range from 20 nm to 250 nm is preferred (the latter range now recited in new claim 9). Applicants argue that the skilled artisan would not conclude that perfringolysin-O and streptolysin-O have the same size without actual data or at the very least, more convincing arguments. Further, any comparison of protein size should be made as taught in applicants specification, namely photon correlation spectroscopy. The actual size of a protein can

differ from its crystal structure size by several mechanisms, so crystal structure, by itself, is not definitive of the size or dimensions of a protein. Neither Lou, Rossjohn, nor Weis, singly or combined, teach a method for producing protein-coated polystyrene microparticles comprising the steps of combining a suspension of uncoated micropoarticles with a protein having a size from 10 to 300 nm as determined by photon correlation spectroscopy, coating the protein onto the microparticles by adsortion at a pH between 10.5 and 12.5, and separating the non-adsorbed protein from the protein-coated microparticles.

In light of the present amendments and the above remarks, the examiner's reconsideration of the rejection of claims 1 and 2 under 35 USC §103 is respectfully requested by Applicants.

Claim 5 has been rejected under 35 USC §103 (a) as being unpatentable over Vaynberg in light of Bocquier and Bohidar , or, alternatively, over Lou in light of Weis and Rossjohn, and further in view of Bangs, Pure & Appl. Chem. 10, 1873-1879 (hereinafter "Bangs"). The examiner states that Vaynberg and Lou fail to teach microparticles that have a magnetizable core; however Bangs teaches microparticles that have a magnetizable core and their utility in separation of solid and liquid phases. The examiner argues that therefore it would have been obvious to one of ordinary skill in the art to include the microparticles having a magnetizable core as taught by Bangs in the method for producing protein-coated polystryene microparticles of Vaynberg or, alternatively, Lou.

Applicants argue that the examiners case for obviousness has not been made. Applicants have argued above with regard to the patentability of claim 1, from which claim 5 depends, and they argue that claim 5 should enjoy the same patentability. In light of the present amendments and the above remarks, the examiner's reconsideration of the rejection of claim 5 under 35 USC §103 is respectfully requested by Applicants.

Applicants submit that their application is now in condition for allowance, and favorable reconsideration of their application in light of the above amendments and remarks is respectfully requested. Allowance of claims 1-3, 5, and 9-19 at an early date is earnestly solicited.

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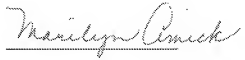
Respectfully submitted,



Marilyn L. Amick
Reg. No. 30,444

Customer No. 23690
Phone: 317-521-7561
Fax: 317-521-2883

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Respectfully submitted,

Marilyn Amick

Marilyn L. Amick
Reg. No. 30,444

Customer No. 23690
Phone: 317-521-7561
Fax: 317-521-2883